IQWiG Reports – Commission No. A19-23

Rucaparib (ovarian cancer; maintenance treatment) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Rucaparib (Ovarialkarzinom; Erhaltungstherapie) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.1; Status: 7 August 2019). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BRCA	breast cancer associated gene
CA-125	cancer antigen-125
CI	confidence interval
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DRS-P	Disease-Related Symptoms Subscale – Physical
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
EQ-5D	European Quality of Life-5 Dimensions
ESMO	European Society for Medical Oncology
FACT	Functional Analysis of Cancer Therapy
FOSI-18	FACT Ovarian Symptom Index-18
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HRD	homologous recombination deficiency
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MID	minimally important difference
MRI	magnetic resonance imaging
non-tBRCA	negative test for BRCA mutation, but positive test for other mutations in the tumour
PET	positron emission tomography
PFS	progression-free survival
PT	Preferred Term
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
tBRCA	BRCA mutation found in the tumour
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug rucaparib. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 26 February 2019.

Research question

The aim of the present report was the assessment of the added benefit of rucaparib as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy in comparison with the appropriate comparator therapy (ACT).

For the benefit assessment, the research question presented in Table 2 resulted from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of rucaparib

Research question	Therapeutic indication	ACT[a]
1	Adult patients with platinum-sensitive relapsed high-grade epithelial ovarian cancer[b] who are in response (complete or partial) to platinum-based chemotherapy	Watchful waiting
a: Presentation of the respective ACT specified by the G-BA. b: This term also includes fallopian tube and primary peritoneal cancer. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

In the present dossier assessment, the term "ovarian cancer" includes ovarian, fallopian tube and primary peritoneal cancer.

The company named watchful waiting as ACT and thus followed the G-BA's specification.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Results

Study pool

The ARIEL3 study was included in the benefit assessment.

Study design

The ARIEL3 study was a double-blind, randomized parallel-group study on the comparison of rucaparib versus placebo. The study included adult patients with platinum-sensitive relapse of high-grade serous or endometrioid epithelial ovarian cancer who had achieved complete or partial response to prior platinum-containing chemotherapy. Patients were to be in good to slightly impaired general condition at baseline (Eastern Cooperative Oncology Group Performance Status [ECOG PS] of 0 to 1).

The study included a total of 564 patients, randomized in a 2:1 ratio either to treatment with rucaparib (N = 375) or placebo (N = 189). Treatment with rucaparib was conducted in compliance with the German approval status. Patients were treated until disease progression according to the Response Evaluation Criteria in Solid Tumours (RECIST), unacceptable toxicity or withdrawal of consent.

The primary outcome of the study was progression-free survival (PFS). Patient-relevant secondary outcomes were overall survival, health status, symptoms and adverse events (AEs).

Depending on the outcomes, the benefit assessment was based on the first or second data cut-off. The final data cut-off was planned for the time point after the death of 70% of the patients. Due to imprecise results on overall survival and the fact that positive effects were largely limited to the outcome "PFS", among other aspects, the European Medicines Agency (EMA) granted conditional approval for rucaparib. This also corresponds to the recommendations of the European Society for Medical Oncology (ESMO) Consensus Conference of 2017, according to which results on PFS should always be interpreted together with results on additional outcomes including patient-reported outcomes. Considering the results on PFS alone is deemed inadequate, however.

Implementation of the appropriate comparator therapy in the ARIEL3 study

The included ARIEL3 study was not designed for a comparison with watchful waiting, but, with limitations, is still suitable for such a comparison.

A main limitation in the implementation of the ACT watchful waiting in the ARIEL3 study was the fact that regular examinations with imaging techniques were planned for the diagnosis of disease progression. This may lead to a systematically premature diagnosis of disease progression. However, since patients do not benefit from an earliest possible initiation of subsequent therapy, the S3 guideline recommends a symptom-oriented approach without regular examination intervals.

It can be considered an approximation to watchful waiting that the time of diagnosis of disease progression (diagnosed with imaging techniques) was significantly earlier than the time of initiation of subsequent therapy. Between the time of diagnosis of disease progression with imaging techniques and the initiation of subsequent therapy, there was a period of about 2 months in both treatment arms. This shows that decisions on providing patients with

subsequent therapies were not based solely on the diagnosis of disease progression using imaging techniques.

Risk of bias and certainty of conclusions

The risk of bias across outcomes was rated as low for the ARIEL3 study. At the outcome-specific level, the results of all outcomes, except for the outcomes "overall survival" and "discontinuation due to AEs", were rated as having a high risk of bias.

In summary, the certainty of conclusions of the results of all outcomes was low due to the limitations regarding the implementation of the ACT. Based on the available data, at most hints, e.g. of an added benefit, can therefore be determined for all outcomes.

Results

Mortality

Overall survival

There was no statistically significant difference between the treatment groups for the outcome "all-cause mortality". This resulted in no hint of an added benefit of rucaparib in comparison with the ACT watchful waiting; an added benefit is therefore not proven.

Morbidity

Health status (European Quality of Life-5 Dimensions [EQ-5D] visual analogue scale [VAS])

The mean difference at treatment cycle 3 compared with baseline was considered for the outcome "health status" recorded with the EQ-5D VAS. There was a statistically significant difference to the disadvantage of rucaparib. However, the 95% confidence interval (CI) of Hedges' g was not completely outside the irrelevance range [−0.2; 0.2]. It can therefore not be inferred that the effect was relevant. This resulted in no hint of an added benefit of rucaparib in comparison with the ACT watchful waiting for this outcome; an added benefit is therefore not proven.

Symptoms (Disease-Related Symptoms Subscale – Physical [DRS-P] of the Functional Analysis of Cancer Therapy [FACT] Ovarian Symptom Index-18 [FOSI-18])

The mean difference at treatment cycle 3 compared with baseline was considered for the outcome "symptoms" recorded with the DRS-P subscale of the FOSI-18. There was a statistically significant difference to the disadvantage of rucaparib. In addition, the 95% CI for Hedges' g was fully outside the irrelevance range [−0.2; 0.2]. This was interpreted to be a relevant effect. Hence, there was a hint of lesser benefit in comparison with the ACT watchful waiting for this outcome.

Health-related quality of life

The dossier contained no data for health-related quality of life. This resulted in no hint of an added benefit of rucaparib in comparison with the ACT watchful waiting for this outcome; an added benefit is therefore not proven.

Side effects

Severe adverse events (CTCAE grade ≥ 3), serious adverse events and discontinuation due to adverse events

Statistically significant differences to the disadvantage of rucaparib were shown between the treatment arms for each of the outcomes "severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)" and "discontinuation due to AEs". This resulted in a hint of greater harm from rucaparib in comparison with the ACT watchful waiting for each of the outcomes "severe AEs (CTCAE grade ≥ 3)" and "discontinuation due to AEs".

In contrast, there was no statistically significant difference between the treatment groups for the outcome "SAEs". Hence, for this outcome, there was no hint of greater or lesser harm from rucaparib in comparison with watchful waiting; greater or lesser harm for this outcome is therefore not proven.

Specific adverse events

Musculoskeletal and connective tissue disorders, general disorders and administration site conditions, gastrointestinal disorders, photosensitivity reaction, dysgeusia, and blood and lymphatic system disorders (CTCAE grade ≥ 3)

There was a statistically significant difference in favour of rucaparib for the AE outcome "musculoskeletal and connective tissue disorders". This effect of this outcome from the category of non-serious/non-severe side effects was no more than marginal, however. Hence, for this AE outcome, there was no hint of greater or lesser harm from rucaparib in comparison with the ACT watchful waiting; greater or lesser harm is therefore not proven.

There was a statistically significant difference to the disadvantage of rucaparib for each of the AE outcomes "general disorders and administration site conditions", "gastrointestinal disorders", "photosensitivity reaction", "dysgeusia", and "blood and lymphatic system disorders" (CTCAE grade ≥ 3). This resulted in a hint of greater harm from rucaparib in comparison with the ACT watchful waiting for each of these outcomes.

Myelodysplastic syndrome and acute myeloid leukaemia

No statistically significant difference between the treatment groups was shown for each of the specific AEs "myelodysplastic syndrome" and "acute myeloid leukaemia". This resulted in no hint of greater or lesser harm from rucaparib in comparison with the ACT watchful waiting for either of these outcomes; greater or lesser harm is therefore not proven for these outcomes.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Based on the results presented, probability and extent of the added benefit of the drug rucaparib in comparison with the ACT are assessed as follows:

In the overall consideration, there were only negative effects of different extents for rucaparib in comparison with watchful waiting, each with the probability "hint". These mainly concerned outcomes on side effects of different severity grades. A negative effect was also shown for symptoms recorded with the DRS-P. However, due to the present situation of a comparison with watchful waiting, it is conceivable that the observed negative effect in this outcome was also more due to treatment-related side effects and less to changes in disease-specific symptoms.

Due to the high number of censored patients, no informative results were available for the outcome "overall survival", so that, against this background, the negative result in the area of side effects cannot be interpreted meaningfully.

In summary, there is no hint of an added benefit of rucaparib in comparison with the ACT watchful waiting for adult patients with platinum-sensitive relapsed high-grade epithelial ovarian cancer who are in response (complete or partial) to platinum-based chemotherapy; an added benefit is therefore not proven.

Table 3 presents a summary of the probability and extent of the added benefit of rucaparib.

Table 3: Rucaparib – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with platinum-sensitive relapsed high-grade epithelial ovarian cancer[b] who are in response (complete or partial) to platinum-based chemotherapy	▪ Watchful waiting	Added benefit not proven[c]
a: Presentation of the ACT specified by the G-BA. b: This term also includes fallopian tube and primary peritoneal cancer. c: Only patients with an ECOG PS of 0 or 1 were included in the relevant study. It remains unclear whether the observed effects can be transferred to patients with an ECOG PS of ≥ 2. ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee		

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

The approach for deriving an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report was the assessment of the added benefit of rucaparib as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy in comparison with the ACT.

For the benefit assessment, the research question presented in Table 4 resulted from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of rucaparib

Research question	**Therapeutic indication**	**ACT[a]**
1	Adult patients with platinum-sensitive relapsed high-grade epithelial ovarian cancer[b] who are in response (complete or partial) to platinum-based chemotherapy	Watchful waiting
a: Presentation of the respective ACT specified by the G-BA. b: This term also includes fallopian tube and primary peritoneal cancer. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

According to the S3 guideline “Diagnostics, Therapy and Follow-up of Malignant Ovarian Tumours”, cancers of the ovaries, fallopian tubes, and peritoneum are jointly classified due to the same pathogenesis and histomorphology [3]. In the present dossier assessment, the term “ovarian cancer” therefore includes ovarian, fallopian tube and peritoneal cancer.

The company named watchful waiting as ACT and thus followed the G-BA’s specification.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) were used for the derivation of the added benefit.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on rucaparib (status: 26 February 2019)
- bibliographical literature search on rucaparib (last search on 17 January 2019)
- search in trial registries for studies on rucaparib (last search on 17 December 2018)

To check the completeness of the study pool:

- bibliographical literature search on rucaparib (last search on 12 March 2019)

The check identified no additional relevant study.

2.3.1 Studies included

The study listed in the following Table 5 was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: rucaparib vs. watchful waiting

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
CO-338-014 (ARIEL3[b])	Yes	Yes	No
a: Study sponsored by the company. b: In the following tables, the study is referred to with this abbreviated form. RCT: randomized controlled trial; vs.: versus			

Section 2.6 contains a reference list for the study included.

2.3.2 Study characteristics

2.3.2.1 Description of the study design of the ARIEL3 study

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the study included – RCT, direct comparison: rucaparib vs. watchful waiting

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
ARIEL3	RCT, double-blind, parallel	Adult women ≥ 18 years with platinum-sensitive[b] high-grade (grade 2/3) serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer who have achieved response to prior platinum-based chemotherapy[c], ECOG-PS 0 or 1	Rucaparib (N = 375) placebo (N = 189)	Screening: ≤ 120 days before randomization Treatment: until disease progression according to RECIST, toxicity, withdrawal of consent Observation[d]: outcome-specific, until death, loss to follow-up, withdrawal of consent or end of study	87 centres in Australia, Belgium, Canada, France, Germany, Israel, Italy, New Zealand, Spain, United Kingdom, USA 4/2014–ongoing Data cut-offs ▪ 15 Apr 2017 (primary analysis) ▪ 31 Dec 2017 (AEs)	Primary: PFS Secondary: overall survival, health status, symptoms, AEs

a: Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b: Defined as disease progression > 6 months after last dose of penultimate platinum-containing chemotherapy (see Table 7).
c: Evidence of complete or partial response to recent platinum-based treatment (randomization ≤ 8 weeks after the last dose of platinum therapy).
d: Outcome-specific information is provided in Table 8: primary analysis after 70% of the patients from the tBRCA subgroup had a progression event according to RECIST.

AE: adverse event; BRCA: breast cancer associated gene; ECOG PS: Eastern Cooperative Oncology Group Performance Status; N: number of randomized patients; PFS: progression-free survival; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria in Solid Tumours; tBRCA: tumour BRCA; vs.: versus

Table 7: Characteristics of the interventions – RCT, direct comparison: rucaparib vs. watchful waiting

Study	Intervention	Comparison
ARIEL3	Rucaparib 600 mg (starting dose)[a], 2x daily at 12-hour intervals, continuous treatment (28-day cycle)	Placebo[a], 2x daily at 12-hour intervals, continuous treatment (28-day cycle)
	Pretreatment required: ▪ ≥ 2 platinum-based treatment regimens (1 thereof immediately before maintenance treatment with rucaparib) ▫ penultimate platinum-containing chemotherapy decisive for definition as platinum-sensitive with disease progression ≥ 6 months after the last dose of platinum-containing chemotherapy ▫ most recent platinum-containing chemotherapy had to be a platinum-containing combination therapy, with partial or complete response; last dose within 8 weeks before study inclusion allowed: ▪ ≤ 1 non-platinum-based therapy (neoadjuvant + adjuvant treatment were considered together as 1 regimen) ▪ hormonal therapy (not counted as non-platinum-based therapy) ▪ maintenance treatment after chemotherapeutic regimen allowed, with the exception of the most recent treatment regimen before baseline not allowed: ▪ PARP inhibitors including rucaparib **Concomitant treatment** allowed: ▪ supportive therapy (antiemetics, analgesics) ▪ continued hormonal therapy for pretreated breast cancer ▪ chemotherapy, radiotherapy, antibody therapy, gene therapy, vaccination, angiogenesis inhibitors (≤ 14 days before the first dose of the study medication and during the study) ▪ erythropoietin, darbepoetin alfa, and/or haematopoietic colony-stimulating factors ▪ bisphosphonates ▪ low molecular weight heparin (warfarin with caution) not allowed: ▪ antineoplastic treatments such as chemotherapy, antibody or other immunotherapy, radiotherapy or other novel agents	
a: Dose adjustments of rucaparib/placebo: ▫ interruption in case of grade 3-4 haematological or non-haematological toxicity (except alopecia, nausea, vomiting, adequately treated diarrhoea) ▫ resumed treatment in case of improvement to grade ≤ 2 toxicity, with same or reduced dose (stepwise to 480 mg, 360 mg or 240 mg 2x daily, in case of returned toxicity), at the investigator's discretion ▫ treatment discontinuation if interruption > 14 days or further toxicity after 2 reduction steps PARP: poly(adenosine diphosphate-ribose) polymerase; RCT: randomized controlled trial; vs.: versus		

The ARIEL3 study was a double-blind, randomized parallel-group study on the comparison of rucaparib versus placebo. The study included adult patients with platinum-sensitive relapse of high-grade serous or endometrioid epithelial ovarian cancer who had achieved complete or partial response to prior platinum-containing chemotherapy. Patients were to be in good to slightly impaired general condition at baseline (ECOG PS of 0 to 1).

The study included a total of 564 patients, randomized in a 2:1 ratio either to treatment with rucaparib (N = 375) or placebo (N = 189). Randomization was stratified by type of homologous recombination deficiency (HRD) of the tumour (BRCA mutation found in the tumour [tBRCA]/patients who tested negative for BRCA mutation, but positive for other mutations in the tumour [non-tBRCA]/biomarker negative]), time to disease progression following the last dose of the penultimate platinum-containing chemotherapy before study inclusion (6 to 12 months/> 12 months), and best response to most recent platinum-containing chemotherapy before study inclusion (complete or partial).

Treatment with rucaparib was conducted in compliance with the German approval status [4].

Patients were treated until disease progression according to RECIST, unacceptable toxicity or withdrawal of consent. Following disease progression according to RECIST, the patient and physician could be unblinded individually upon request to the sponsor. It was not allowed to switch from the placebo arm to treatment with rucaparib after disease progression.

The primary outcome of the study was PFS. Patient-relevant secondary outcomes were overall survival, health status, symptoms and AEs.

Data cut-offs

Two data cut-offs were analysed in the ARIEL3 study:

- First data cut-off on 15 April 2017: primary analysis after 70% of the patients from the tBRCA subgroup had a progression event according to RECIST
- Second data cut-off on 31 December 2017: interim analysis in the framework of the European approval process for the outcomes “PFS2” and side effect outcomes

The primary PFS data cut-off was planned and data from it were available for all patient-relevant outcomes for the benefit assessment. In addition, data from the second data cut-off were available for side effect outcomes.

In summary, the data cut-offs with the last analyses of the outcomes included were used for the benefit assessment. This was the first data cut-off for all patient-relevant outcomes except side effect outcomes, for which the second data cut-off was used.

The time point of the final analysis for the outcome “overall survival” in the ARIEL3 study was planned for the time point when 70% of the study patients have died. According to information provided in the European Public Assessment Report (EPAR), this time point is expected to be reached in 2022. Since the EMA considered the analyses for overall survival from the data cut-off from 15 April 2017 as not informative due to the large proportion of censored patients, and positive effects were largely limited to the outcome “PFS”, rucaparib was granted conditional approval [5]. The company was required to provide data from the final analysis for the outcome “overall survival”, on the basis of which a final assessment would then be made. This approach

corresponds to the recommendations of the ESMO Consensus Conference of 2017, according to which results on PFS should always be interpreted together with results on additional outcomes including patient-reported outcomes [6]. Considering the results on PFS alone is deemed inadequate, however.

2.3.2.2 Implementation of the appropriate comparator therapy in the ARIEL3 study

Operationalization of watchful waiting

For the present benefit assessment, watchful waiting was operationalized as a follow-up strategy, which comprises both diagnosis of relapse according to the S3 guideline [3] and, if required, its treatment. In essence, the S3 guideline recommends a symptom-oriented approach without regular examination intervals. It advises against the routine use of device-based diagnostics and marker determination in symptom-free patients. Physical and gynaecological examinations are recommended instead. If an elevated level of cancer antigen-125 (CA-125) has been measured in asymptomatic patients nonetheless, this should not be decisive for the diagnosis of a relapse, but further diagnostics should be decided upon in consultation with the patient. Consultation with the patient is generally regarded as one of the most important elements in the care of patients with ovarian cancer, also when deciding on subsequent therapies. According to the guideline, computed tomography (CT), positron emission tomography (PET), PET/CT and magnetic resonance imaging (MRI) have been established as imaging procedures, for example if relapse is suspected due to symptoms.

Implementation of watchful waiting in the ARIEL3 study

The included ARIEL3 study was not designed for a comparison with watchful waiting, but, with limitations, is still suitable for such a comparison.

A main limitation in the implementation of the ACT watchful waiting in the ARIEL3 study was the fact that regular examinations with imaging techniques were planned for the diagnosis of disease progression. This may lead to a systematically premature diagnosis of disease progression. It can be assumed that already a progress of the disease can be detected by means of device-based diagnostics, but that the patient is still symptom-free at the time of the imaging test. However, according to current data, an earlier start of subsequent therapy is not associated with a prolongation of overall survival, but rather leads to an earlier deterioration in quality of life [7]. Hence, the S3 guideline recommends a symptom-oriented approach without regular examination intervals [3]. The study documents do not describe to what extent regular clinical examinations also include gynaecological examinations.

However, it can be considered an approximation to watchful waiting that the time of diagnosis of disease progression (diagnosed with imaging techniques) was significantly earlier than the time of initiation of subsequent therapy. In the rucaparib arm, the median time to reaching the primary outcome “PFS” was 10.8 months, while the median time to initiation of the first subsequent therapy after discontinuation of the study treatment was 12.5 months. In the placebo arm, the median time to reaching the primary outcome “PFS” was 5.4 months, while the median

time to initiation of the first subsequent therapy after discontinuation of the study treatment was 7.4 months. Hence, between the time of diagnosis of disease progression with imaging techniques and the initiation of subsequent therapy, there was a total period of about 2 months in both treatment arms. These results show that decisions on providing patients with subsequent therapies were not based solely on the diagnosis of disease progression using imaging techniques. However, the study documents contained no information on the extent to which the initiation of subsequent therapy was linked to the presence of disease symptoms.

In summary, the approach used in the ARIEL3 study was assessed as sufficient implementation of the ACT and the study was used for the benefit assessment. Due to the described aspects, the certainty of conclusions of the study is limited, however. Based on the available data, at most hints, e.g. of an added benefit, can therefore be determined for all outcomes.

2.3.2.3 Planned duration of follow-up observation in the ARIEL3 study

Table 8 shows the planned duration of follow-up observation in the included study for the individual outcomes.

Table 8: Planned duration of follow-up observation – RCT, direct comparison: rucaparib vs. watchful waiting

Study **Outcome category** **Outcome**	**Planned follow-up observation**
ARIEL3	
Mortality	
Overall survival	Every 12 weeks until death, loss to follow-up, withdrawal of consent or end of study
Morbidity	
Health status (EQ-5D VAS)	Up to 28 days after the last dose of the study medication
Symptoms (DRS-P subscale of the FOSI-18)	Up to 28 days after the last dose of the study medication
Health-related quality of life	No usable data
Side effects	
All outcomes in the category "side effects"[a]	Up to 28 days after the last dose of the study medication
a: Deviating from this, the adverse events of special interest "acute myeloid leukaemia" and "myelodysplastic syndrome" were observed until death, loss to follow-up, withdrawal of consent or end of study. DRS-P: Disease-Related Symptoms Subscale – Physical; EQ-5D: European Quality of Life-5 Dimensions; FOSI-18: Functional Analysis of Cancer Therapy Ovarian Symptom Index-18; RCT: randomized controlled trial; VAS: visual analogue scale; vs.: versus	

Except for the outcome "overall survival" and individual specific AEs, the observation periods for the outcomes recorded in the ARIEL3 study were systematically shortened because their recording was only planned for the period of treatment with the study medication (plus 28 days).

To be able to draw a reliable conclusion on the total study period or the time until death of the patients, it would be necessary, however, to record all outcomes over the total period of time.

2.3.2.4 Patient characteristics and course of the study

Table 9 shows the characteristics of the patients in the study included.

Table 9: Characteristics of the study population – RCT, direct comparison: rucaparib vs. watchful waiting

Study Characteristics Category	**Rucaparib**	**Placebo[a]**
ARIEL3	N[b] = 375	N[b] = 189
Age [years], mean (SD)	60.5 (9.3)	60.7 (9.7)
Ethnicity, n (%)		
White	302 (80.5)	149 (78.8)
Non-white	26 (6.9)[c]	13 (6.9)[c]
Geographical region, n (%)		
North America	132 (35.2)	70 (37.0)
Western Europe	183 (48.8)	94 (49.7)
Other	60 (16.0)[c]	25 (13.2)[c]
Histology, n (%)		
Serous	357 (95.2)	179 (94.7)
Endometrioid	16 (4.3)	7 (3.7)
Other	2 (0.5)[c]	3 (1.6)
Primary tumour location, n (%)		
Ovaries	312 (83.2)	159 (84.1)
Fallopian tubes	32 (8.5)	10 (5.3)
Primary peritoneum	31 (8.3)	19 (10.1)
Other	0 (0)	1 (0.5)
Histological grade (two tier), n (%)		
High grade	375 (100.0)	189 (100.0)
Number of previous chemotherapies, n (%)		
2	231 (61.6)	124 (65.6)
3	108 (28.8)	42 (22.2)
4	23 (6.1)	17 (9.0)
> 4	13 (3.5)[c]	6 (3.2)[c]
Number of previous platinum-containing chemotherapies, n (%)		
2	236 (62.9)	126 (66.7)
3	109 (29.1)	47 (24.9)
> 3	30 (8.0)	16 (8.5)

(continued)

Table 9: Characteristics of the study population – RCT, direct comparison: rucaparib vs. watchful waiting (continued)

Study **Characteristics** **Category**	**Rucaparib**	**Placebo**[a]
ARIEL3	N[b] = 375	N[b] = 189
ECOG PS, n (%)		
0	280 (74.7)	136 (72.0)
1	95 (25.3)	53 (28.0)
Disease duration: time between first diagnosis and randomization [months], mean (SD)	48.3 (32.3)	46.4 (28.4)
Time to progression after penultimate platinum-containing chemotherapy, n (%)		
≥ 6–12 months	153 (40.8)	68 (36.0)
> 12–24 months	140 (37.3)	74 (39.2)
> 24 months	82 (21.9)	47 (24.9)
Objective response to most recent platinum-containing chemotherapy, n (%)		
CR	126 (33.6)	64 (33.9)
PR	249 (66.4)	125 (66.1)
Treatment discontinuation[d], n (%)	285 (76.0)	180 (95.2)
Study discontinuation, n (%)	ND	ND

a: Sufficient approximation to the ACT watchful waiting, but with limitations (see Section 2.3.2.2).
b: Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
c: Institute's calculation.
d: Data cut-off on 15 April 2017.

CR: complete response; ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; M: male; n: number of patients in the category; N: number of randomized (or included) patients; ND: no data; PR: partial response; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The characteristics of the total population were sufficiently comparable between both treatment groups. The mean age of the patients in the ARIEL3 study was about 61 years, and the majority were white. About half of the study participants were from Western Europe. A clear majority of the study participants had a tumour with serous histology localized in the ovaries. Over 60% of the patients had been pretreated with at least 2 platinum-containing chemotherapeutic regimens. Since the ARIEL3 study only included patients with good to slightly impaired general condition (ECOG PS from 0 to 1), no conclusions can be drawn for patients with worse general condition (ECOG PS 2 or higher).

Treatment duration and observation period

Table 10 shows the mean/median treatment duration of the patients.

Table 10: Information on the course of the study – RCT, direct comparison: rucaparib vs. watchful waiting

Study **Duration of the study phase** **Outcome category**	**Rucaparib**	**Placebo[a]**
ARIEL3	N = 372	N = 189
Treatment duration [months]		
Median [min; max]	8.3 [0; 35]	5.5 [0; 35]
Mean (SD)	10.4 (7.97)	6.4 (4.89)
Observation period [months]		
Overall survival	ND	ND
Morbidity	ND	ND
Health-related quality of life	ND	ND
Side effects	ND	ND

a: Sufficient approximation to the ACT watchful waiting, but with limitations (see Section 2.3.2.2).
ACT: appropriate comparator therapy; max: maximum; min: minimum; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The treatment duration in the rucaparib arm of the ARIEL3 study was about 34% longer than in the placebo arm. The difference in treatment duration between the study arms was caused by different treatment discontinuation rates, which were mainly due to disease progression.

The company's dossier contained no information on the observation periods of individual outcomes. It was assumed for these outcomes, however, that the difference in observation duration and treatment period between the arms were of a similar size if these outcomes were not observed indefinitely, as was the case for overall survival and some specific AEs (see Table 8 for planned follow-up observation).

2.3.2.5 Risk of bias across outcomes (study level)

Table 11 shows the risk of bias across outcomes (risk of bias at study level).

Table 11: Risk of bias across outcomes (study level) – RCT, direct comparison: rucaparib vs. watchful waiting

Study	**Adequate random sequence generation**	**Allocation concealment**	**Blinding**		**Reporting independent of the results**	**No additional aspects**	**Risk of bias at study level**
			Patients	**Treating staff**			
ARIEL3	Yes	Yes	Yes	Yes	Yes	Yes	Low

RCT: randomized controlled trial; vs.: versus

The risk of bias across outcomes was rated as low for the ARIEL3 study. This concurs with the company's assessment.

Irrespective of this, the certainty of conclusions of the ARIEL3 study was restricted as the ACT was implemented only to a limited extent (see Section 2.3.2.2).

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.7.4.3.2 of the full dossier assessment):

- Mortality
  - overall survival
- Morbidity
  - health status measured with the EQ-5D VAS
  - symptoms measured with the DRS-P of the FOSI-18
- Health-related quality of life
  - no data were recorded for this outcome
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - myelodysplastic syndrome
  - acute myeloid leukaemia
  - if applicable, further specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 B) (see Section 2.7.4.3 of the full dossier assessment).

Table 12 shows for which outcomes data were available in the study included.

Table 12: Matrix of outcomes – RCT, direct comparison: rucaparib vs. watchful waiting

Study	Outcomes									
	Overall survival	Health status (EQ-5D VAS)	Symptoms (DRS-P subscale of the FOSI-18)	Health-related quality of life	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade ≥ 3)	Myelodysplastic syndrome (PT)	Acute myeloid leukaemia (PT)	Further specific AEs[a]
ARIEL3	Yes	Yes	Yes	No[b]	Yes	Yes	Yes	Yes	Yes	Yes

a: The following events (MedDRA coding) are considered: "musculoskeletal and connective tissue disorders (SOC, AE)"; "general disorders and administration site conditions (SOC, AE)", "gastrointestinal disorders (SOC, AE)", "photosensitivity reaction (PT, AE)", "dysgeusia (PT, AE)" and "blood and lymphatic system disorders (SOC, severe CTCAE grade ≥ 3 AEs)".

b: Outcome not recorded; the company allocated the FOSI-18 instrument to health-related quality of life (see Section 2.7.4.3.2 of the full dossier assessment).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; DRS-P: Disease-Related Symptoms Subscale – Physical; EQ-5D: European Quality of Life-5 Dimensions; FOSI-18: Functional Analysis of Cancer Therapy Ovarian Symptom Index-18; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

2.4.2 Risk of bias

Table 13 describes the risk of bias for the results of the relevant outcomes.

Table 13: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: rucaparib vs. watchful waiting

Study	Study level	Outcomes									
		Overall survival	Health status (EQ-5D VAS)	Symptoms (DRS-P subscale of the FOSI-18)	Health-related quality of life	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade ≥ 3)	Myelodysplastic syndrome (PT)	Acute myeloid leukaemia (PT)	Further specific AEs[a]
ARIEL3	L	L	H[b]	H[b]	-[c]	H[d]	L[e]	H[d]	H[d]	H[d]	H[d]

a: The following events (MedDRA coding) are considered: "musculoskeletal and connective tissue disorders (SOC, AE)"; "general disorders and administration site conditions (SOC, AE)", "gastrointestinal disorders (SOC, AE)", "photosensitivity reaction (PT, AE)", "dysgeusia (PT, AE)" and "blood and lymphatic system disorders (SOC, severe CTCAE grade ≥ 3 AEs)".
b: Large proportion of patients (> 10%) who were not considered in the analysis.
c: Outcome not recorded; the company allocated the FOSI-18 instrument to health-related quality of life (see Section 2.7.4.3.2 of the full dossier assessment).
d: Incomplete observations for potentially informative reasons.
e: Despite low risk of bias, a restricted certainty of results was assumed for the outcome "discontinuation due to AEs" (see Section 2.7.4.2 of the full dossier assessment).
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; DRS-P: Disease-Related Symptoms Subscale – Physical; EQ-5D: European Quality of Life-5 Dimensions; FOSI-18: Functional Analysis of Cancer Therapy Ovarian Symptom Index-18; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

The results of all outcomes, except for the outcomes "overall survival" and "discontinuation due to AEs", had a high risk of bias. The results for the outcomes "health status" and "symptoms" had a high risk of bias due to the large proportions of patients (> 10%) not considered in the analysis. For the results of all AEs, except for the outcome "discontinuation due to AEs", the assessment of a high risk of bias was due to potentially informative censoring.

This deviates from the assessment of the company, which assessed the risk of bias for all outcomes in the outcome category of side effects as low.

The certainty of conclusions for the outcome "discontinuation due to AEs" was restricted despite low risk of bias (see Section 2.7.4.2 of the full dossier assessment).

Overall assessment of the certainty of conclusions

In summary, the certainty of conclusions of the results of all outcomes was low due to the limitations regarding the implementation of the ACT (see Section 2.3.2.2).

Based on the available data, at most hints, e.g. of an added benefit, can therefore be determined for all outcomes.

2.4.3 Results

Table 14 and Table 15 summarize the results of the comparison of rucaparib with placebo in adult patients with platinum-sensitive relapsed high-grade epithelial ovarian cancer who are in response (complete or partial) to platinum-based chemotherapy. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. If available, Kaplan-Meier curves on the outcomes included are presented in Appendix A of the full dossier assessment. Results on common AEs are presented in Appendix B of the full dossier assessment.

Table 14: Results (mortality, side effects, time to event) – RCT, direct comparison: rucaparib vs. watchful waiting

Study **Outcome category** **Outcome**	**Rucaparib**		**Placebo[a]**		**Rucaparib vs. placebo[a]**
	N	**Median time to event in months [95% CI]** **Patients with event n (%)**	**N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**HR [95% CI]; p-value[b]**
ARIEL3					
Mortality					
Overall survival	375	29.6 [28.6; NC] 81 (21.6)	189	NA [27.2; NC] 42 (22.2)	0.88 [0.60; 1.28]; 0.504
Side effects					
AEs (additional information)	372	0.1 [0.07; 0.10] 372 (100)	189	0.3 [0.16; 0.46] 182 (96.3)	–
SAEs	372	NA 83 (22.3)	189	NA 20 (10.6)	1.45 [0.88; 2.40]; 0.143
Severe AEs (CTCAE grade ≥ 3)	372	5.1 [3.71; 7.79] 222 (59.7)	189	42.0 [21.98; NC] 30 (15.9)	4.33 [2.93; 6.40]; < 0.001
Discontinuation due to AEs	372	NA [38.1; NC] 61 (16.4)	189	NA 4 (2.1)	5.55 [2.00; 15.40]; 0.001
Musculoskeletal and connective tissue disorders (AE, SOC)	372	13.8 [8.8; 19.2] 172 (46.2)	189	7.3 [5.9; 10.9] 86 (45.5)	0.74 [0.57; 0.96]; 0.026

(continued)

Table 14: Results (mortality, side effects, time to event) – RCT, direct comparison: rucaparib vs. watchful waiting (continued)

Study Outcome category Outcome	Rucaparib N	Rucaparib Median time to event in months [95% CI] Patients with event n (%)	Placebo[a] N	Placebo[a] Median time to event in months [95% CI] Patients with event n (%)	Rucaparib vs. placebo[a] HR [95% CI]; p-value[b]
General disorders and administration site conditions (AE, SOC)	372	0.9 [0.7; 1.1] 296 (79.6)	189	3.8 [2.4; 5.7] 108 (57.1)	1.70 [1.36; 2.12]; < 0.001
Gastrointestinal disorders (AE, SOC)	372	0.1 [0.1; 0.2] 344 (92.5)	189	1.8 [1.1; 2.8] 146 (77.2)	2.22 [1.81; 2.72]; < 0.001
Photosensitivity reaction (AE, PT)	372	NA 68 (18.3)	189	NA 1 (0.5)	26.32 [3.64; 190.22]; 0.001
Dysgeusia (AE, PT)	372	NA 148 (39.8)	189	NA 13 (6.9)	6.69 [3.79; 11.81]; < 0.001
Blood and lymphatic system disorders (SOC, CTCAE grade ≥ 3)	372	NA [NC; NC] 95 (25.5)	189	NA [21.9; NC] 3 (1.6)	14.87 [4.70; 47.04]; < 0.001
Myelodysplastic syndrome (AE, PT)	372	NA 2 (0.5)	189	NA 0 (0)	NC
Acute myeloid leukaemia (AE, PT)	372	NA 1 (0.3)	189	NA 0 (0)	NC

a: Sufficient approximation to the ACT watchful waiting, but with limitations (see Section 2.3.2.2).
b: HR, CI, p-value: Cox proportional hazards model stratified by HRD classification, best response to most recent platinum-based regimen before start of maintenance treatment, and interval between completion of the penultimate platinum-based regimen and disease progression.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; DRS-P: Disease-Related Symptoms Subscale – Physical; HR: hazard ratio; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Table 15: Results (morbidity) – RCT, direct comparison: rucaparib vs. watchful waiting

Study Outcome category Outcome	Rucaparib			Placebo[a]			Rucaparib vs. placebo[a]
	N[b]	Values at baseline mean (SD)	Change at treatment cycle 3[c] mean (SE)[d]	N[b]	Values at baseline mean (SD)	Change at treatment cycle 3[c] mean (SE)[d]	MD [95% CI]; p-value[d]
ARIEL3							
Morbidity							
Health status EQ-5D VAS[e]	270	79.3 (13.94)	−4.8 (1.05)	148	77.8 (15.41)	1.0 (1.78)	−4.4 [−7.0; −1.8]; 0.001 Hedges' g: −0.34 [−0.54; −0.14][f]
Symptoms (DRS-P subscale of the FOSI-18)[e]	273	29.3 (4.37)	−2.8 (0.33)	149	29.2 (4.89)	−0.5 (0.39)	−2.3 [−3.1; −1.5]; < 0.001 Hedges' g: −0.57 [−0.78; −0.37][f]
Health-related quality of life							
Outcome not recorded[g]							

a: Sufficient approximation to the ACT watchful waiting, but with limitations (see Section 2.3.2.2).
b: Number of patients considered in the analysis for the calculation of the effect estimation; baseline values may be based on other patient numbers.
c: One treatment cycle lasted 28 days.
b: ANCOVA adjusted for HRD classification, best response to most recent platinum-based regimen before start of maintenance treatment, and interval between completion of the penultimate platinum-based regimen and disease progression.
e: A positive change from the start until the end of the study indicates improvement; a positive effect estimation indicates an advantage for the intervention.
f: Institute's calculation based on MD and CI of the ANCOVA.
g: The company allocated the FOSI-18 instrument to health-related quality of life (see Section 2.7.4.3.2 of the full dossier assessment).

ANCOVA: analysis of covariance; CI: confidence interval; DRS-P: Disease-Related Symptoms Subscale – Physical; EQ-5D: European Quality of Life-5 Dimensions; FOSI-18: Functional Analysis of Cancer Therapy Ovarian Symptom Index-18; MD: mean difference; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; VAS: visual analogue scale; vs.: versus

As shown in Section 2.3.2.2, based on the available data, at most hints, e.g. of an added benefit, can be determined for all outcomes due to the limited implementation of the ACT.

For the morbidity outcomes (EQ-5D VAS, DRS-P subscale of the FOSI-18), analyses of cycle 3 were used in the present benefit assessment because the results at later time points were not usable due to the large proportion of patients not included in the analyses (> 30%). Since observed differences between the treatment arms were already clearly visible during the first 3 treatment cycles, however, a conclusion on benefit is possible despite the short observation period (see Sections 2.7.4.2 and 2.7.4.3.2 of the full dossier assessment).

Mortality

There was no statistically significant difference between the treatment groups for the outcome "all-cause mortality". This resulted in no hint of an added benefit of rucaparib in comparison with the ACT watchful waiting; an added benefit is therefore not proven.

This concurs with the company's assessment.

Morbidity

Health status (VAS of the EQ-5D)

The mean difference at treatment cycle 3 compared with baseline was considered for the outcome "health status" recorded with the EQ-5D VAS. There was a statistically significant difference to the disadvantage of rucaparib. However, the 95% CI of Hedges' g was not completely outside the irrelevance range [−0.2; 0.2]. It can therefore not be inferred that the effect was relevant. This resulted in no hint of an added benefit of rucaparib in comparison with the ACT watchful waiting for this outcome; an added benefit is therefore not proven.

The result of this assessment concurs with that of the company, which used the time to first deterioration with an unvalidated minimally important difference (MID) for the derivation of the added benefit (see Section 2.7.4.3.2 of the full dossier assessment).

Symptoms (DRS-P subscale of the FOSI-18)

The mean difference at treatment cycle 3 compared with baseline was considered for the outcome "symptoms" recorded with the DRS-P subscale of the FOSI-18. There was a statistically significant difference to the disadvantage of rucaparib. In addition, the 95% CI for Hedges' g was fully outside the irrelevance range [−0.2; 0.2]. This was interpreted to be a relevant effect. Hence, there was a hint of lesser benefit in comparison with the ACT watchful waiting for this outcome.

The company allocated the DRS-P subscale of the FOSI-18 to health-related quality of life (see next section).

Health-related quality of life

The dossier contained no data for health-related quality of life (see Section 2.7.4.3.2 of the full dossier assessment). This resulted in no hint of an added benefit of rucaparib in comparison with the ACT watchful waiting for this outcome; an added benefit is therefore not proven.

The result of this assessment concurs with that of the company, which considered results both on the DRS-P subscale of the FOSI-18 and on the FOSI-18 total score for this outcome. Due to a missing validation, the company did not use these results for the derivation of the added benefit, however, but only presented a description of the results in Module 4 B.

Side effects

Severe adverse events (CTCAE grade ≥ 3), serious adverse events and discontinuation due to adverse events

Statistically significant differences to the disadvantage of rucaparib were shown between the treatment arms for each of the outcomes "severe AEs (CTCAE grade ≥ 3)" and "discontinuation due to AEs". This resulted in a hint of greater harm from rucaparib in comparison with the ACT watchful waiting for each of the outcomes "severe AEs (CTCAE grade ≥ 3)" and "discontinuation due to AEs".

In contrast, there was no statistically significant difference between the treatment groups for the outcome "SAEs". Hence, for this outcome, there was no hint of greater or lesser harm from rucaparib in comparison with watchful waiting; greater or lesser harm for this outcome is therefore not proven.

This deviates from the assessment of the company, which conducted a summarizing analysis of the side effect outcomes and overall derived no added benefit for treatment with rucaparib in comparison with watchful waiting.

Specific adverse events

Musculoskeletal and connective tissue disorders, general disorders and administration site conditions, gastrointestinal disorders, photosensitivity reaction, dysgeusia, and blood and lymphatic system disorders (CTCAE grade ≥ 3)

There was a statistically significant difference in favour of rucaparib for the AE outcome "musculoskeletal and connective tissue disorders". This effect of this outcome from the category of non-serious/non-severe side effects was no more than marginal, however (see Section 2.5.1). Hence, for this AE outcome, there was no hint of greater or lesser harm from rucaparib in comparison with the ACT watchful waiting; greater or lesser harm is therefore not proven.

A statistically significant difference to the disadvantage of rucaparib was shown for each of the following AE outcomes: general disorders and administration site conditions; gastrointestinal disorders, photosensitivity reaction, dysgeusia, and blood and lymphatic system disorders (with CTCAE grade ≥ 3). This resulted in a hint of greater harm from rucaparib in comparison with the ACT watchful waiting for each of these outcomes.

This deviates from the assessment of the company, which, apart from myelodysplastic syndrome and acute myeloid leukaemia, used no further specific AEs for the derivation of the added benefit.

Myelodysplastic syndrome and acute myeloid leukaemia

No statistically significant difference between the treatment groups was shown for each of the specific AEs "myelodysplastic syndrome" and "acute myeloid leukaemia". This resulted in no

hint of greater or lesser harm from rucaparib in comparison with the ACT watchful waiting for either of these outcomes; greater or lesser harm is therefore not proven for these outcomes.

This concurs with the company's assessment.

2.4.4 Subgroups and other effect modifiers

The following subgroup characteristics were relevant for the present assessment:

- age (< 65; 65 to 74; ≥ 75)
- mutation status (tBRCA; non-tBRCA; biomarker-negative)
- time to disease progression after the penultimate platinum-containing chemotherapy before baseline (6 to 12 months; > 12 months)
- best response to most recent platinum-containing chemotherapy before baseline (complete; partial)
- geographical region (North America; Western Europe; Australia/New Zealand; Israel)
- disease severity at baseline (measurable disease; no disease)
- number of prior chemotherapeutic regimens (2; 3; ≥ 4)

Subgroup analyses were only used if each subgroup comprised at least 10 people and, for binary data, if at least 10 events had occurred in one of the subgroups. Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. Moreover, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

Altogether, no relevant effect modifications were observed for the considered subgroup characteristics. This concurs with the approach of the company, which also determined no relevant effect modifications on the basis of the subgroup characteristics considered by the company.

2.5 Probability and extent of added benefit

The derivation of probability and extent of the added benefit is presented below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.5.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4 (see Table 16).

Determination of the outcome category for outcomes on symptoms and side effects

It could not be inferred from the dossier for all outcomes considered in the present benefit assessment whether they were non-serious/non-severe or serious/severe. The classification of these outcomes is justified below.

Determination of the outcome category for the outcome "symptoms"

The outcome "symptoms", recorded with the DRS-P subscale of the FOSI-18, was rated as non-serious/non-severe outcome. It could not be inferred from the company's documents whether the patients' symptoms were in a range that is to be rated as serious/severe. In addition, there was no information on absolute threshold values of the DSR-P scale that mark a transition from non-severe to severe manifestation of a symptom or late complication.

Determination of the outcome category for the outcome "discontinuation due to adverse events"

The outcome "discontinuation due to AEs" was allocated to the outcome category of serious/severe side effects. A comparison with the available listings in the study documents showed that the documented treatment discontinuations were mostly (56%) due to severe side effects (CTCAE grade ≥ 3).

Determination of the outcome category for the outcomes on specific adverse events

The following specific AEs were allocated to the category of non-serious/non-severe side effects because the events included in these outcomes were mostly non-serious/non-severe: musculoskeletal and connective tissue disorders, general disorders and administration site conditions, gastrointestinal disorders, photosensitivity reaction, and dysgeusia. Regarding the outcome "blood and lymphatic system disorders", only CTCAE grade ≥ 3 events, hence only serious/severe events, were used for the derivation of the added benefit.

Table 16: Extent of added benefit at outcome level: rucaparib vs. watchful waiting

Outcome category **Outcome**	**Rucaparib vs. placebo[a]** **Median time to event (months) or mean change from baseline until treatment cycle 3 or proportion of events (%)** **Effect estimation [95% CI]; p-value** **Probability[b]**	**Derivation of extent[c]**
Mortality		
All-cause mortality	Median: 29.6 vs. NA HR: 0.88 [0.60; 1.28]; p = 0.504	Lesser benefit/added benefit not proven
Morbidity		
EQ-5D VAS		
Change at treatment cycle 3	Mean: −4.8 vs. 1.0 MD: −4.4 [−7.0; −1.8]; p = 0.001 Hedges' g: −0.34 [−0.54; −0.14]	Lesser benefit/added benefit not proven
Symptoms (DRS-P subscale of the FOSI-18)		
Change at treatment cycle 3	Mean: −2.8 vs. −0.5 MD: −2.3 [−3.1; −1.5]; p < 0.001 Hedges' g: −0.57 [−0.78; −0.37][d] probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications lesser benefit, extent: "non-quantifiable"
Health-related quality of life		
Outcome not recorded[e]		
Side effects		
SAEs	NA vs. NA HR: 1.45 [0.88; 2.40]; p = 0.143	Greater/lesser harm not proven
Severe AEs (CTCAE grade ≥ 3)	Median: 5.1 vs. 42.0 HR: 4.33 [2.93; 6.40]; p < 0.001 HR: 0.23 [0.16; 0.34][f] probability: "hint"	Outcome category: serious/severe side effects CI_u < 0.75; risk ≥ 5% greater harm, extent: "major"
Discontinuation due to AEs	NA vs. NA HR: 5.55 [2.00; 15.40]; p = 0.001 HR: 0.18 [0.06; 0.50][f] probability: "hint"	Outcome category: serious/severe side effects CI_u < 0.75; risk ≥ 5% greater harm, extent: "major"
Musculoskeletal and connective tissue disorders (AE, SOC)	Median: 13.8 vs. 7.3 HR: 0.74 [0.57; 0.96]; p = 0.026	Outcome category: non-serious/non-severe side effects 0.90 ≤ CI_u < 1.00 greater/lesser harm not proven[g]
General disorders and administration site conditions (AE, SOC)	Median: 0.9 vs. 3.8 HR: 1.70 [1.36; 2.12]; p < 0.001 HR: 0.59 [0.47; 0.74][f] probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: "considerable"

(continued)

Table 16: Extent of added benefit at outcome level: rucaparib vs. watchful waiting (continued)

Outcome category **Outcome**	**Rucaparib vs. placebo[a]** **Median time to event (months) or mean change from baseline until treatment cycle 3 or proportion of events (%)** **Effect estimation [95% CI]; p-value** **Probability[b]**	**Derivation of extent[c]**
Gastrointestinal disorders (AE, SOC)	Median: 0.1 vs. 1.8 HR: 2.22 [1.81; 2.72]; p < 0.001 HR: 0.45 [0.37; 0.55][f] probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: "considerable"
Photosensitivity reaction (AE, PT)	NA vs. NA HR: 26.32 [3.64; 190.22]; p = 0.001 HR: 0.04 [0.01; 0.27][f] probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: "considerable"
Dysgeusia (AE, PT)	NA vs. NA HR: 6.69 [3.79; 11.81]; p < 0.001 HR: 0.15 [0.08; 0.26][f] probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: "considerable"
Blood and lymphatic system disorders (SOC, CTCAE grade ≥ 3)	NA vs. NA HR: 14.87 [4.70; 47.04]; p < 0.001 HR: 0.07 [0.02; 0.21][f] probability: "hint"	Outcome category: serious/severe side effects CI_u < 0.75; risk ≥ 5% greater harm, extent: "major"
Acute myeloid leukaemia (AE, PT)	NA vs. NA 0.3% vs. 0% HR: NC	Greater/lesser harm not proven
Myelodysplastic syndrome (AE, PT)	NA vs. NA 0.5% vs. 0% HR: NC	Greater/lesser harm not proven

a: Sufficient approximation to the ACT watchful waiting, but with limitations (see Section 2.3.2.2).
b: Probability given if statistically significant differences are present.
c: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
d: If the CI of Hedges' g is fully outside the irrelevance range [−0.2; 0.2], this is interpreted to be a relevant effect. In other cases, the presence of a relevant effect cannot be derived.
e: The company allocated the FOSI-18 instrument to health-related quality of life (see Section 2.7.4.3.2 of the full dossier assessment).
f: Institute's calculation, reversed direction of effect to enable use of limits to derive the added benefit.
g: Extent of the observed effect no more than marginal.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; DRS-P: Disease-Related Symptoms Subscale – Physical; EQ-5D: European Quality of Life-5 Dimensions; FOSI-18: Functional Analysis of Cancer Therapy Ovarian Symptom Index-18; HR: hazard ratio; MD: mean difference; MedDRA: Medical Dictionary for Regulatory Activities; NA: not achieved; NC: not calculable; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

2.5.2 Overall conclusion on added benefit

Table 17 summarizes the results considered in the overall conclusion on the extent of the added benefit.

Table 17: Positive and negative effects from the assessment of rucaparib in comparison with watchful waiting

Positive effects	Negative effects
▫ -	Non-serious/non-severe symptoms/late complications ▪ symptoms: hint of lesser benefit – extent: "non-quantifiable"
	Serious/severe side effects ▪ severe AEs (CTCAE grade ≥ 3): hint of greater harm – extent: "major" ▫ including blood and lymphatic system disorders: hint of greater harm – extent: "major" ▪ discontinuation due to AEs: hint of greater harm – extent "major"
	Non-serious/non-severe side effects ▪ specific AEs: hint of greater harm – extent: "considerable" (general disorders and administration site conditions, gastrointestinal disorders, photosensitivity reaction, and dysgeusia)
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events	

In the overall consideration, there were only negative effects of different extents for rucaparib in comparison with watchful waiting, each with the probability "hint". These mainly concerned outcomes on side effects of different severity grades. A negative effect was also shown for symptoms recorded with the DRS-P. However, due to the present situation of a comparison with watchful waiting, it is conceivable that the observed negative effect in this outcome was also more due to treatment-related side effects and less to changes in disease-specific symptoms.

Due to the high number of censored patients, no informative results were available for the outcome "overall survival", so that, against this background, the negative result in the area of side effects cannot be interpreted meaningfully.

In summary, there is no hint of an added benefit of rucaparib in comparison with the ACT watchful waiting for adult patients with platinum-sensitive relapsed high-grade epithelial ovarian cancer who are in response (complete or partial) to platinum-based chemotherapy; an added benefit is therefore not proven.

The result of the assessment of the added benefit of rucaparib in comparison with the ACT is summarized in Table 18.

Table 18: Rucaparib – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adult patients with platinum-sensitive relapsed high-grade epithelial ovarian cancer[b] who are in response (complete or partial) to platinum-based chemotherapy	▪ Watchful waiting	Added benefit not proven[c]

a: Presentation of the ACT specified by the G-BA.
b: This term also includes fallopian tube and primary peritoneal cancer.
c: Only patients with an ECOG PS of 0 or 1 were included in the relevant study. It remains unclear whether the observed effects can be transferred to patients with an ECOG PS of ≥ 2.
ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee

The assessment described above deviates from that of the company, which derived an indication of considerable added benefit.

The approach for deriving an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.6 List of included studies

ARIEL-3

Clovis Oncology. A study of rucaparib as switch maintenance following platinum-based chemotherapyin patients with platinum-sensitive, high-grade serous or endometrioid epithelial ovarian, primary peritoneal or fallopian tube cancer (ARIEL3): study results [online]. In: ClinicalTrials.gov. 28.03.2019 [Accessed: 06.05.2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT01968213.

Clovis Oncology. A multicenter, randomized, double-blind, placebo-controlled phase 3 study of rucaparib as switch maintenance following platinum-based chemotherapy in patients with platinum-sensitive, high-grade serous or endometrioid epithelial ovarian, primary peritoneal or fallopian tube cancer [online]. In: EU Clinical Trials Register. [Accessed: 22.03.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2013-000518-39.

Clovis Oncology. A study of rucaparib as switch maintenance following platinum-based chemotherapyin patients with platinum-sensitive, high-grade serous or endometrioid epithelial ovarian, primary peritoneal or fallopian tube cancer (ARIEL3): study details [online]. In: ClinicalTrials.gov. 29.11.2018 [Accessed: 22.03.2019]. URL: https://clinicaltrials.gov/ct2/show/NCT01968213.

Clovis Oncology. Phase III Studie zu Rucaparib als Switch-Erhaltungstherapie nach Platin bei rezidiviertem hochgradigem serösem und endometrioidem Ovarialkrebs (ARIEL3) [online]. In: Deutsches Register Klinischer Studien. 14.04.2015 [Accessed: 22.03.2019]. URL: http://www.drks.de/DRKS00006376.

Clovis Oncology. A multicenter, randomized, double-blind, placebo-controlled phase 3 study of rucaparib as switch maintenance following platinum-based chemotherapy in patients with platinum-sensitive, high-grade serous or endometrioid epithelial ovarian, primary peritoneal or fallopian tube cancer: study CO-338-014; Zusatzanalysen [unpublished]. 2017.

Clovis Oncology. A multicenter, randomized, double-blind, placebo-controlled phase 3 study of rucaparib as switch maintenance following platinum-based chemotherapy in patients with platinum-sensitive, high-grade serous or endometrioid epithelial ovarian, primary peritoneal or fallopian tube cancer: study CO-338-014; clinical study report [unpublished]. 2017.

Coleman RL, Oza AM, Lorusso D, Aghajanian C, Oaknin A, Dean A et al. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2017; 390(10106): 1949-1961.

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Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a19-23-rucaparib-ovarian-fallopian-tube-or-peritoneal-cancer-maintenance-treatment-benefit-assessment-according-to-35a-social-code-book-v.11859.html.